Journal of research in health science
Volume 9-10 issue. 4 2020, pp. 38-47
ISSN 2523-1251 (Online) ISSN 2523-1243 (Print)
JOURNAL DOI 10.37057/2523-1251
www.journalofresearch.org
info@journalofresearch.org

SJIF 2020: 6.224
IFS 2020 4.085

The role and the possibility of adoptive immunotherapy in conjunction with chemotherapy in ovarian cancer.

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Objective: To analyze the efficacy of adoptive immunotherapy in advanced ovarian cancer.

Materials and Methods: Adoptive (adoptive - adscititious)immunoterapiya- carried out to increase the number of natural killer cells. We observed - 18 patients with ovarian cancer. Age - an average of 54,4 ± 0,5 years. By the beginning of lactose local tumor immunotherapy process was widespread and in addition to pathological effusions into the peritoneal and/or pleural cavity of patients also had other manifestations of multiple cancer lesions. Treatment efficacy was assessed by the terms of accumulation of fluid, the level of the marker CA-125 in the blood, according to X-ray and ultrasound, have also been studied immunological parameters. For the LAC-immunotherapy abdominal cavity was drained catheter for 2-4 weeks. From exudate generated LAC.
All patients received 1-3 courses LAK immunotherapy. Each course consisted of 5-20 intraperitoneal injection of IL-2 in a dose of 0.5-1.0 million IU and 8.2 LAC injection of 50-100 million cells.

Results: During the LAK therapy was noted the death and subsequent disappearance of the effusion of tumor cells in the background of increasing numbers of activated lymphoid cells (more than 80% of patients), decreased levels of tumor marker CA-125 (50%), and there was partial regression of the tumor (13%). In three cases, after the first course of chemotherapy in combination with the LAC marked 75% tumor regression and disappearance of ascites. A month after the end of the LAC-immunotherapy effect was maintained in 89% (-57% full and partial 32%) patients. In 100% of patients showed normalization of the relation (CD4 \ CD8).

Conclusions: The study showed the effectiveness of the proposed method of adoptive immunotherapy in patients with metastatic ovarian cancer. An important positive aspect is the possibility of drug treatment after an effective immunotherapy.

The article analyzes various combinations of multiple primary tumors of the female reproductive system.

As a result, a hypothesis was formulated about three main syndromes: hormone-dependent, radio-induced and viral-dependent polyneoplasia.

Primarily multiple tumors of the reproductive system organs.

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The urgency of the problem of multiple primary tumors of the reproductive system and colon is determined by several interrelated causes and circumstances: the increase in the population of so-called diseases of civilization (anovulation, infertility, obesity, diabetes mellitus), changes in sexual behavior (early onset of sexual activity, promiscuity) and increased cancer incidence. Some progress in early detection and treatment of cancer has resulted in increased survival rates. These factors led to an increase in the real clinical value of synchronous and metachronic polyneoplasia.

In determining the signs of primary tumor multiplicity, we were guided by the criteria proposed by Warren and Gates (1932) [19] and clarified by N.N.Petrov (1947) [9], according to which each of the tumors should have a clear picture of malignancy, be separate from the other and not be metastases.

Many authors noted a natural prevalence of multiple primary tumors of the reproductive system among all types of polyneoplasia in women [1, 6, 8, 11, 13, 18, 20]. Annegers, Malkasian (1981) [12] conducted a thorough study of other tumors in 1192 endometrial cancer patients treated at the Mayo Brothers Clinic (Rochester, USA). Primarily multiple tumors were found in 18.1%. An increase in breast cancer risk was noted in patients with common pathogenetic factors: infertility and obesity. Nemeth et al. (1978) [16] studied polyneoplasia in 1366 patients with uterine body cancer. The frequency of synchronous and metachronic tumors was 2.2%. Synchronous tumors were most often ovarian cancer, while metachronous tumors were breast cancer or uterine, colorectal carcinoma.

We studied the data concerning 18 800 patients with malignant tumors of the uterus body (2157), breast (8167), cervical (3812), ovarian (1992), colon (2072), vulva (520) and vagina (80) available at the Petrov Scientific Research Institute of Oncology for the period from I960 to 1999. In 714 cases, among this number of patients' primary multiplicity of malignant tumors (3,8%) was revealed (Table 1).

In the analysis of various combinations of primary stagnant tumors, 75% of them were classified as hormone- and diet-dependent, 11% as radio-induced tumors, and 9% as viral-dependent polyneoplasia. Other observations accounted for no more than 5% of all cases.

Table 1. Distribution of primary multiple malignant tumours

Localizing the first tumour	Number of patients	Of them with a second tumor.				
		uterine body	mammary gland	Ovaries	uterine cervix	large intestine

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	n	%	n	%	n	%	n	%	n	%	n	%
uterine body	258	100	-	-	96	37,2	74	28,7	25	9,7	63	24,4
mammary gland	251	100	96	38,3	-	-	67	26,7	42	16,7	46	18,3
Ovaries	155	100	74	47,8	67	43,2	-	-	5	3,2	9	5,8
uterine cervix	100	100	25	25	42	42	5	3,2	-	-	28	28
large intestine	146	100	63	43,1	46	31,5	9	6,2	28	19,2	-	-

Hormone-dependent adenocarcin syndrome as part of polyneoplasia.

Among the variety of different localizations of polyneoplasia of the reproductive system and colon in women in terms of frequency and real clinical importance are undoubtedly hormonal and diet-dependent malignant tumors.

It has been established that the general risk factors for hormone-dependent tumors of the reproductive system organs (uterine, breast and ovarian cancers) are pronounced chronic hyperestrogenia, which is especially typical for patients with uterine body cancer. The high content of progesterone receptors, the synthesis of which is stimulated by estrogens in RTM, RM and RN patients, is a positive prognostic factor, which reliably correlates with higher 5-year survival rates. Patients with colorectal cancer have no reliable signs of estrogen dependence.

The pathogenetic community of hormone-dependent tumors of the reproductive system and colorectal cancer (and especially colorectal cancer) is explained by endocrine disorders of metabolic character.

Among 2157 patients with uterine body cancer, 297 (13.8%) have multiple primary tumors verified. Breast cancer ranks first (32.3% in relation to polyneoplasia), which underlines the greatest pathogenetic similarity of these two tumors in the syndrome of hormone-dependent primary multiple tumors. At the same time, there are pronounced disorders in both reproductive and energy homeostats. In particular, the predominance of the I hormone-dependent type of RTM (according to Ya.V. Bohman's

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classification) [4-6], adrenal and involutive types of RTM (according to V.F. Semiglazov's classification) [10] was noted (Table 2).

Synchronous combinations of RTM and RN, noted in 74 observations (24.9%), are characterized by pronounced disorders in the reproductive system with no significant changes in metabolism.

Among 8167, primary breast cancer patients polyorganic primary multiple tumors were noted in 312 (3.8%). As in primary RTM patients, a natural combination of the same tumors - breast cancer, uterine body and colon cancer - are noted in 80.5% of such observations.

Hormone-dependent polyneoplasia syndrome is characterized by either synchronism or short intervals (2-3 years) between clinical manifestations of breast, uterine and ovarian cancer. It could be assumed that the metachronism of these tumors seems to be the same - in fact, they can occur synchronously, but are diagnosed at short intervals due to the different growth rates of different tumors, which by their pathogenetic characteristics form a clearly defined syndrome (Table 3).

Among 1992 patients with primary ovarian cancer, polyneoplasia was morphologically verified in 191 (9.6%). The characteristic combination with endometrial adenocarcinomas (38.7% concerning all multiple primary tumors), breast (35.1%) and colon (4.7%) together amounted to 78.5%, while the frequency of all other tumors did not exceed that expected in the general population.

The exceptional aggressiveness of ovarian cancer determines the detection of this tumor, as a rule, in stages III and IV (up to 70%) and doubtful prognosis. Therefore, in the composition of polyneoplasia, NS is either detected as a synchronous tumor or as a second tumor. A frequent combination of endometrioid ovarian cystadenocarcinoma and endometrial cancer has been observed, which emphasizes their pathogenetic similarity. Analysis of combinations of endometrioid ovarian cystadenocarcinoma and RTM confirms the position that different localization of the endometrium (in the uterine mucosa or in heterotopic zones) does not exclude similarity of their biological behavior, up to the possibility of synchronous malignization under the influence of common etiological factors. Classified ovarian cyst-denocarcinoma is more often combined with breast carcinoma.

Table 2. Pathogenetic type of uterine body cancer versus the frequency of primary multiple breast and ovarian cancers

Pathogenetic type of uterine body	Number of patients	Of them with breast carcinoma.	Of those with ovarian carcinoma.

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cancer		n	%±m	п	%±m
I (hormone dependent) II (autonomous)	1456 701	84 12*	5,8±2,5 1,7±3,7	64 10*	4,4±2,6 1,4±3,7
Total	2157	96	4,4±2,1	74	3,4±2,1

Note: * - the difference is reliable but compared with I (hormone-dependent type) of uterine body cancer, $p<0.05$.

Table 3: Average intervals between detection of the first and subsequent tumor (in years)

Localization	Localization of the second tumor		
First tumor	uterine body	mammary gland	Ovaries
uterine body	-	2,1	0
mammary gland	3,0	-	6,0
mammary gland	0	3,2	-

Thus, common for the three tumors - RTM, RM and RH - are ovulation disorders and chronic hyperestrogenia (anovulation in RTM and RMH patients, ovulation hyper-stimulation in RH patients), infertility. Most of these combinations fall on the hill-dependent pathogenetic types of RTM and RTM, which is important for the justification of factors and the formation of risk groups.

Many authors paid attention to the rare combination of various localizations of gynecological cancer and neoplasms of the large intestine, but there was no adequate explanation of this phenomenon. Among 2072 primary colorectal cancer patients (PCC) we observed polyorganic primary multiple tumors were found in 164 (7,9%). In the vast majority of these observations (89.1%!), RTK was combined with uterine, ovarian and breast adenocarcinomas. All other combinations are single observations and certainly

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had a random coincidence character. Strange as it may seem at first glance, the combination with stomach carcinoma was found in only 1.8% of uterine cancer.

The frequency of obesity increases significantly in the combination of uterine and breast tumours with colon carcinoma (81.8%), while in combination with rectal tumours it is 47.8%, i.e. 1.7 times less common ($p<0.05$).

For the first time, features concerning colorectal cancer have been revealed: 65.8% of its combinations are hormone-dependent and only 34.2% - autonomous ($p<0.05$). Very different ratios have been established in patients with rectal cancer as part of polyneoplasia: the ratio of I (hormone-dependent) and II (autonomous) types of RTM is expressed in figures of 40% and 60% ($p<0.05$). Consequently, the majority of rectal cancer patients had no anovulation, hyperestrogenia and endocrine-exchange disorders. There are good reasons to assume the pathogenetic polymorphism of cancer that occurs in different parts of the large intestine. A combination of data suggests that most colorectal tumours are hormone-dependent. However, this hypothesis cannot be argued concerning the pathogenesis of colorectal cancer.

In studying the results of treatment of hormone-dependent polyneoplasia, an unexpected, but almost extremely important feature has been established. It has two main aspects.

First, not only metachronic but also synchronous detection of various combinations of cancer of the uterus, breast, ovaries and colon, as a rule, does not prevent the adequate treatment of each tumor. Treatment planning is structured in such a way that the main emphasis is placed on a radical treatment program for the most aggressive and more common tumor.

Secondly, if the adequate treatment plan is sufficiently implemented, the prognosis of hormone-dependent polyneoplasia is generally not worse than the corresponding solitary tumors of the same stages. This first established fact, which emphasizes the importance of timely detection of polyneoplasia and their adequate treatment, can be explained by the following circumstances. First of all, it is noteworthy that there is a real possibility to detect some tumors which are part of polyneoplasia (especially ovarian cancer) on the average at an earlier stage than the corresponding solitary neoplasms. Another explanation is the pathogenetic features of hormone-dependent polyneoplasia. Endocrine-exchange disorders in patients with ovarian cancer, breast cancer and especially uterine cancer may play a dual and paradoxical role, chronologically changing from tumor transformation to its progression. During the carcinogenesis phase, the symptomatic complex of reproductive and energy homeostasis disorders increases the risk of cancer of the uterus, ovaries and breast. At the same time,

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at the stage of progression and metastasis, the role of this syptomocomplex becomes diametrically opposite, causing a greater hormonosaviousness and hormone sensitivity of both solitary and primary multiple tumors, and thus their lesser autonomy and aggressiveness.

Estimates of the relative probability of second tumor development (relative risk - RR), representing the ratio of the observed cumulative risk (OR) in the study group to the expected incidence in the population (expected risk - ER) over the same period, were determined over 1.5, 10 and 15 years.

In patients with uterine body cancer, the relative risk of breast cancer is 13.6 in the first year, 5.3 in the fifth, 3.9 in the tenth and 3.0 in the fifteenth. In breast cancer patients, the relative risk of uterine body cancer is 9.0 in the first year, 2.4 in the fifth, 2.2 in the tenth and 3.6 in the fifteenth. Therefore, in both breast cancer and RTM patients, the risk of the second tumor development is realized mainly in the first year, i.e. due to synchronous polyneoplasia. Further, during all 15 years the expected probability exceeds the observed one reliably ($p<0,05$), which allows concluding about a higher risk of hormone-dependent polyneoplasiasiasis in MM and RTM patients in comparison with the risk in healthy woman (fig.1).

The main risk factors of hormone-dependent polyneoplasia development are the age of 40-69 years and early stage of the first tumor. The latter circumstance finds a simple explanation in a favorable prognosis of these patients and a long period of their lives, during which the risk of metachronous tumor is realized.

Each individual factor that characterizes endocrine metabolic disorders does not increase the risk of either solitary or primary multiple tumors. The combination of different disorders in reproductive and energy homeostats creates a real risk of RTM and RMW. Three factors in these two systems increase the risk of a solitary tumor, and 4-5 and more increase the risk of mountain monoplasia syndrome. At the same time, when ovarian cancer occurs in polyneoplasia, the main disorders are concentrated in reproductive homeostatus, and when combined with colon carcinoma, metabolic disorders prevail.

It can be concluded that the system of simple and accessible diagnostic tests integrated into the system of an in-depth examination of patients with breast cancer and RTM, allows timely detection of hormone-dependent polyneoplasia.

Syndrome of radio-induced polyneoplasia

Metachronous polyneoplasia of the rectum, vagina and uterine body, which occurred 5 years or more after radiation treatment of cervical cancer, are considered. Primary multiple tumors were detected in 192 (5.0%) of primary DSM patients treated at

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the Petrov Scientific Research Institute of Oncology. 24 observations of rectal cancer (12.5% about all polyneoplasia), 46 - vaginal cancer (23.9%), 25 - uterine body cancer (13.0%) and 12 - uterine body sarcomas (6.7%) were attributed to radioinduced tumors. Besides, in 15 cases, rectal cancer was detected in the distant future after combined radiation treatment of uterine cancer.

First of all, long intervals between the end of cervical cancer radiotherapy and clinical manifestations of metachrone-like tumor: from 6 to 32 years (Table 4).

The average interval for malignant neoplasms of the uterus body was 12.8 years, ovarian cancer - 11.4 years, vaginal cancer - 16.7 years, rectal cancer - 18.3 years, and between radiation treatment of uterine body cancer and rectal cancer - 13.8 years.

The histotype of the radio-induced tumor was determined by its localization. Direct intestinal tumors had adenocarcinoma structure of different differentiation degree (up to low differentiated cancer), vaginal tumors were represented by flat cell and low differentiated cancer, and uterine body tumors - by two variants: adenocarcinoma or sarcoma (mixed mesodermal tumor).

Since radio-induced vaginal tumors have a similar histological structure to cervical carcinoma, they were traditionally, but mistakenly, considered to be late metastases of DSM.

The following characteristic features of radio-induced polyneoplasia have been established:

- excess of optimal total doses in the vagina and rectum in case of combined radiation treatment of PCM;'.
- associated development of late radial complications: ulcerative rectites and vaginitis;
- dependence of radio-induced cancer on complications of intra-cavity and combined radiation exposure;
- remote exposure before or after surgery does not significantly increase the risk of radio-induced tumours.

Table 4: Sequence and Timing of detection of metachronous primary multiple uterine and colorectal tumours

First tumor	Second tumor				Total
	Uterine body	Uterine body	Uterine body	Uterine body	
Uterine body	-	-	31	15	46

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Uterine cervix		-	-	24	24
Reinal colon	7	-	-	-	7
Direct intestine	10	4	-	-	14
Total	17	4	31	39	91

Calculations of the cumulative relative risk of second radio-induced tumors at different periods of observation, as in the analysis of hormone-dependent polyneoplasia, were made as a result of dividing the observed risk by the expected probability indicator in the population.

For radioinduced vaginal, rectal and uterine cancers, the cumulative relative risk in the 6th year after exposure was 37.5; 11.7 and 12.6, respectively; in the 10th year was 93.4; 48.1; 44.8; in the 20th year was 102.5; 188.2 and 72.6; in the 30th year was 203.6; 104.2 and 116.8, respectively. In the first 10-15 years, the risk of radio-induced tumors is higher in patients of young age (Fig.2).

In general, the real possibility of radio-induced tumors is, all other things being equal, an additional argument in favor of surgical or combined treatment before combined radiation. Metachronic tumors included in the syndrome of radio-induced polyneoplasia regardless of their localization (in the vagina, rectum or uterine body) combines the concentration of adverse prognostic signs in comparison with the corresponding solitary neoplasms. The aggressiveness of radio-induced tumors is due to their reduced degree of differentiation, deep invasion, large size and high potentials for spreading beyond the organ. Previous radiation therapy of uterine cancer leads to expressed fibrosis and trophic disorders of surrounding tissues, which prevents surgical and repeated radiation treatment in a radical volume. Due to these circumstances, 5-year survival rates in patients with all localizations of radio-induced tumors are 15-20% lower than the corresponding solitary tumors.

In patients with radio-induced rectal and uterine tumours, surgical treatment is the method of choice and essentially the second chance of survival. Patients with vaginal metachronous cancer most often have to resort to intra-cavity irradiation and in some cases to posterior pelvic exenteration.

The prognosis depends primarily on the timely detection of the second tumour. Therefore, regular follow-up of uterine cancer patients after combined radiation treatment should be carried out regularly throughout the life of the patient.

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Syndrome of virus-dependent flat celled polyneoplasia of distal parts of female genitalia

The leading role in cervical, vagina and vulva flat cell neoplasms is played by exogenous sexually transmitted factors (infection with the human papilloma virus - HPV - possibly in synergy with the herpes virus 2 serotype). Endogenous factors are of major importance in the etiology and pathogenesis of uterine, ovarian and breast adenocarcinoma. At the same time, patients with receptor-negative endometrial cancer and serous ovarian adenocarcinoma have a high frequency of detection of high oncogenic risk in HPV tumours [2, 3, 14].

The distribution and frequency of risk factors for papillomavirus infection among patients with endometrial receptorinegative cancer and 60% of patients with ovarian adenocarcinoma have been found to be the same in cervical and vulva cancer [15, 17].

The following table presents the incidence of HPV of different types in the examined endometrial cancer patients (Table 5).

Table 5: Frequency of detection of different types of HPV among the examined patients

Types of HPV	Receptor negative cancer		Receptor positive cancer		P
	n	%	n	%	
HPV high oncogenic risk	9	50	3	12	< 0,01
HPV high and low oncogenic risk	2	11,1	1	4	
HPV low oncogenic risk	1	5,6	1	4	
No HPV found.	6	33,3	20	80	< 0,01
Total.	18	100,0	25	100,0	

The table shows that HPV DNA was found in a tumor in 12 of 18 patients with receptor-negative cancer, which is 66.7%. Out of 25 patients with receptor-negative cancer, 20 (80%) did not have HPV DNA in the tumor.

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Papillomavirus was detected in 55% of cases of ovarian tumors with a certain dependence of detection frequency on the histological type (Fig.3).

Human papillomavirus was detected in almost 60% of cases of serous cystadenocarcinoma, in 45% of cases of endometrioid cystadenocarcinoma and 100% of cases of unclassified tumours. The viral etiology of these tumors is also supported by the described combination of these tumors with cervical flat cell cancer. However, further prospective studies are required for the conclusions.

The most apparent common characteristic of a patient with cervical, vaginal and vulvar flat cell cancer is the absence of virgins among them. Common risk factors include early onset of sexual activity (under 16 years), early first birth (under 18 years), promiscuity of the woman and/or her sexual partner. Judging by the peculiarities of the age distribution, the chronology of HPV infection is different for these three tumors. While the peak of dysplasia and Cava in situ are 28-32 years old, for vaginal and vulvar cancers, the peak of the disease shifts to the seventh decade of life. As a result, two factors are involved in the pathogenesis of vaginal and especially vulva cancer: the delayed effect of latent viral infection for several decades and aging, manifested by the involution and dystrophy of the skin and mucous membranes.

Among 192 multiple primary tumors (which occurred in 3812 patients with CMD), 22 observations of vaginal cancer and 21 - vulva cancer were not associated with radiation therapy for cervical cancer (43.3%). With this approach, the established frequency of polyneoplasia of the distal parts of the female genitalia should be recognized as clinically significant, especially since the solitary tumors of the vagina and the vulva occupy no more than 1-4% in the structure of oncogynecological morbidity. From the total number of 43 polyneoplasia of the vulva and vagina, 28 belong to pre-invasive cancer, which completely excludes metastatic combinations. From the rest, 15 observations in 9 initial forms of cancer on the background of dystrophy and dysplasia were revealed, which also indicates the independent nature of these tumors. One more remarkable feature of 43 observations of virus-dependent polyneoplasia is synchronous (in 21 patients) detection with cervical carcinoma or short interval between these tumors (on average - 1.8 years).

Additional information on multiple primary tumors in the distal sections of the female genitalia is provided by analysis of data concerning 520 primary patients with vulva cancer. Polyneoplasia has been detected in 50 patients (9.6%). Among them, pre and micro-invasive cervical cancer were diagnosed in 52% and pre and micro-invasive vaginal cancer in 24%. The other tumors are represented by single casuistic observations. Besides, patients with vulva cancer have a high incidence (20%) of

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multicentric cancer. In general, the comparison of the obtained data allows concluding that the flat epithelium of the cervix, vagina, and vulva represents (using the terminology of Willis, 1954) a single tumor field in which multicentric or polyorgan neoplasms develop under the influence of exogenous factors.

This syndrome is thus characterized mainly by the synchronous occurrence of dysplasia and the initial forms of flat cell cancer developing in a single tumor field. Timely detection of HPV-dependent polyneoplasiasis provides the possibility of organ-preserving treatment methods (cervical conformation, cryo- or laser destruction by vaginal and vulva condition combined with intraepithelial neoplasia) in many young patients. Therefore, understanding the peculiarities of HPV-dependent polyneoplasia sets in motion the system of their diagnosis and treatment, which in many cases can be considered as real secondary prevention of flat cell cancer of the distal parts of female genitalia.